BIOMATERIALS

UDC 615.46:546.41'18

A NEW GENERATION OF CALCIUM PHOSPHATE BIOMATERIALS: THE ROLE OF PHASE AND CHEMICAL COMPOSITIONS

V. I. Putlyaev[1] and T. V. Safronova[1]

Translated from Steklo i Keramika, No. 3, pp. 30 – 33, March, 2006.

Calcium phosphate materials are increasingly applied in the treatment and replacement of bone tissues. The effect of their phase and chemical (ionic) composition on biomedical properties (bioresistivity and bioresorption) of such materials is considered. The principles of the formation of bioceramic microstructure, as well as possible directions for chemical modification of calcium phosphates using biocompatible anions and cations, are discussed.

Hydroxyapatite (HAP) is a calcium phosphate compound constituting the mineral component of the bone. Since calcium and phosphor are the main elements of bones, materials based on calcium phosphate compounds are now used to treat bone tissue defects.

Such materials have to meet certain requirements:

– they should be biocompatible with the living organism;

– depending on the treatment method used, the material should have a certain level of bioresistivity or a certain biodegradation rate;

– in the perfect case, the material should possess biological activity, i.e., have an osteostimulating effect initiating the formation of bone tissue;

– the materials should have a certain strength;

– the materials should withstand various types of sterilization and radiation (UHF, SHF, UV, x-ray, gamma radiation) without changing their properties of biocompatibility, bioresistivity, biodegradability, bioactivity, and strength parameters;

– porous materials should meet certain requirements on the type of porosity and the size of pores, whose diameter should be at least 100 μm, and ensure the desired interaction between the body and the implanted material, i.e., the ingrowth of blood vessels and nerve fibers into the implant;

– osteoplastic materials should be easily amenable to mechanical treatment or other shape-correcting method used in surgery.

Most materials in the $CaO - P_2O_5 - H_2O$ system easily satisfy the requirement of biocompatibility. The presence in the material of CO_3^{2-}, SiO_4^{4-}, Cl^-, F^-, Na^+, K^+, Mg^{2+}, etc., i.e., all ions contained in the natural bone structure or in body tissues, do not disturb biocompatibility.

A biologically compatible material implemented in a living organism does not have a negative effect on tissues, therefore, such implant is not rejected.

Based on their effect on body tissues, biocompatible materials can be classified as biotolerant, bioinert, or bioactive.

Classification of biocompatible materials based on their effect on body tissues

Biotolerant	Metal alloys, polymers
Bioinert	Materials based on aluminum oxide, zirconium dioxide
Bioactive	Materials based on calcium phosphates

The effect of body tissues on implanted materials may differ; accordingly, materials can be classified into biodegradable, bioresistive, and bioresorptive.

Classification of biocompatible materials based on the effect of body tissues on materials

Biodegradable	Metal alloys, polymers
Bioresistive	Materials based on hydroxyapatite
Bioresorptive	Materials bearing tricalcium phosphate or phosphate and silicophosphate glasses

Biodegradability implies the gradual degradation of the structure and properties of a material, and its processing (dissolution) under the effect of the body fluid. Bioresistivity is

[1] M. V. Lomonosov Moscow State University, Moscow, Russia.

TABLE 1

Calcium phosphate	Ca : P ratio	pH interval	SP* at 37°C
Monocalcium phosphate (calcium dihydrophosphate) $Ca(H_2PO_4)_2$	0.50	< 1	Soluble
Dicalcium phosphate dihydrate $CaHPO_4 \cdot 2H_2O$	1.00	2 – 4	$10^{-6.63}$
Dicalcium phosphate (calcium hydrophosphate) $CaHPO_4$	1.00	2 – 4	$10^{-7.02}$
Octacalcium phosphate $Ca_8(HPO_4)_2(PO_4)_4 \cdot 5H_2O$	1.33	6 – 7	$10^{-95.9}$
Hydroxyapatite $Ca_{10}(PO_4)_6(OH)_2$	1.50 – 1.67	> 5	$10^{-117.2}$
Amorphous calcium phosphate	1.33 – 1.67	> 5	Not determ.
Calcium pyrophosphate $Ca_2P_2O_7$	1.00	–	–
Tricalcium phosphate (calcium orthophosphate) $Ca_3(PO_4)_2$	1.50	–	–
Tetracalcium phosphate $Ca_4P_2O_9$	2.00	–	–

* The solubility product (SP) is the product of the concentrations (in respective degrees) of ions in the solution above the precipitate. Thus, for hydroxyapatite $Ca_{10}(PO_4)_6(OH)_2$ $SP = [Ca^{2+}]^{10}[PO_4^{3-}]^6[OH^-]^2 = 10^{-117.2}$.

the property of material characterizing its chemical and structural resistance to the effect of body tissues and fluid. Bioresorption is typical of materials based on calcium- or phosphorus-bearing materials, which in their degradation serve as a source of components for the formation of calcium phosphate in the organism.

The maximum bioresistivity is observed in hydroxyapatite, since its solubility in neutral or weakly alkaline solutions is very low: its solubility product is $10^{-117.2}$. However, on average every 7 years bone tissues in a body are completely renewed due to the equilibrium between soluble and insoluble phosphates in the body [1]. Calcium phosphates and the conditions of their existence in solutions are indicated in Table 1 [2].

As was seen in numerous *in vitro* and *in vivo* experiments of the best studied materials, i.e., hydroxyapatite and tricalcium phosphate $Ca_3(PO_4)_2$ (TCP), calcium phosphate materials, both bioresistive and biodegradable ones, possess biological activity and facilitate the formation of hydroxyapatite after implanting.

The solubility of calcium phosphate materials in model media (acid solutions) or in conditions resembling the conditions in a living organism (for instance, in SBF, that is, simulated body fluid) is well investigated *in vitro*. Solubility increases in the following series: fluorapatite (FAP) → fluorohydroxyapatite (FHAP) → HAP → carbonate-hydroxyapatite (CHAP) → TCP → pyrophosphate (PP) → glasses of the $SiO_2 – CaO – P_2O_5 – X_2O$ system → glasses of the $CaO – P_2O_5 – X_2O$ system (X = Na, K). Furthermore, the above listed compounds may comprise two- and multiphase materials, which obviously expands the above series. The literature contains data on the properties of materials FHAP – HAPO [3], HAP – TCP (U.S. patent No. 6037519), HAP – vitreous phase [4, 5]. Although the authors of the above-mentioned studies consider the bioresistivity and biodegradability of these materials and in some cases also the response of the living body tissues to them, the authors in most cases do not consider the degradation rate as a parameter depending on the phase composition of materials.

A complete analog of human bone tissue, which is a composite material with a complex structure, has not yet been developed. However, the development of materials able to replace the mineral component (spongy bone) is part of today's reality. To obtain such material, it is necessary to form a porous permeable osteoconductive structure with a pore size of 300 μm from a corresponding powder. Such structure after implanting behaves as a matrix for a composite consisting of a porous inorganic (preferably based on a calcium phosphate) component and biogenic tissues. Unfortunately in the case of an injury of a compact or tubular bone that experiences constant sign-variable loads, such interaction with the living organism is hardly possible. A dense material (capable of withstanding high loads) has difficulties in coalescing with natural bone; therefore, craneofacial surgery has to use titanium plates as fixtures [6]. To replace injured areas of bones experiencing loads, titanium rods are used, sometimes coated with a hydroxyapatite layer to decrease the corrosion of metal and the toxic effect of the metal on ambient tissues.

A material could be perfect for bone implant if in service it initially repaired the bone defect and facilitated the formation of the organic bone component and later gradually degraded while remaining a source of phosphorus and calcium to restore the mineral component of the natural bone. The formation of bone tissue is a process proceeding at a certain rate. Consequently, the rate of biodegradation of implanted materials should be consistent with the rate of bone formation, taking into account the method of treatment, the properties of the multiphase material, and the specifics of the interior medium of the body.

The list of inorganic materials for bone implants is rather wide, however, they can be classified based on their phase composition. Control of phase composition is the traditional method for controlling the properties of materials. The phase composition and the mutual position and sizes of the elements (phases) comprising the microstructure of material determine such parameters as strength and density, as well as some other properties of materials that are significant for their application. Based on their phase composition, inorganic materials used for bone implants can be classified into the following groups: I) amorphous, II) glass ceramics; III) polycrystalline.

The phase composition of the first group of biomaterials is represented by glass materials of the system $CaO – P_2O_5$, $CaO – P_2O_5 – X_2O$, $CaO – P_2O_5 – X_2O – SiO_2$, and $CaO – SiO_2 – X_2O$ (X = Na, K).

The biomaterials of group II include glass ceramic materials with an amorphous (vitreous) matrix in which the particles of the crystal phase are distributed. The amorphous phase, similarly to group I, is selected from oxide systems whose components are biologically compatible with body tissues. The main crystalline phases are tricalcium phosphate, hydroxyapatite, and pyrophosphate. In the formation of glass ceramics, such vitreous matrix along with a calcium phosphate crystal phase may also contain apatite, calcium metaphosphate, fluorapatite, calcium diphosphate, as well as fluorophlogopite, diopside, forsterite, anorthite, sphene, wollastonite, and mullite [5].

The phase composition of polycrystalline materials in group III is represented by the crystal phases of hydroxyapatite, tricalciumphosphate, and pyrophosphate. This group yields monosphate and polyphase materials.

There are diverse materials with different phase compositions. Some of the above listed compositions are well studied and described in the literature, not only in the technological context but in the medical context as well (for instance, bioglasses developed by Prof. L. Hench who is the pioneer of this trend [7] or HAP-based monophase ceramics), whereas other materials are insufficiently investigated.

The main principle for controlling properties for the first group of materials is modifying the chemical composition (the additive principle well known for glasses, where the property of glass is calculated taking into account the contributions of its constituent oxides). There are known materials based on glasses of the system $CaO – P_2O_5$, as well as systems $CaO – P_2O_5$, $CaO – P_2O_5 – Na_2O$, $CaO – P_2O_5 – K_2O$, and $CaO – P_2O_5 – Na_2O – MgO – CaF_2$ [8]. The specified glasses are well soluble both in water and in the body fluid. This makes it possible to use the above-mentioned materials in the form of thin glass filaments and tubes, for instance, in neurosurgery. Such glasses can be also recommended for developing biodegradable composites.

The phase composition and, accordingly, the properties of the second group of materials can be controlled by sintering powders (HSP, TCP, etc.) in the presence of a vitreous phase or by the crystallization of a respective glass composition under special conditions. Thus, glass ceramics can be produced using one of two fundamentally different technologies. One of them is traditionally used to obtain ceramic materials from powders; it involves mixing glass powders with HAP or TCP powders and subsequent liquid-phase sintering under thermal treatment at a high temperatures. The other technology implies glass melting, forming desired articles from the glass melt, and their subsequent heat treatment to produce a devitrified (glass ceramic) structure according to a schedule ensuring the formation of crystal seeds and the growth of crystals. The quantities of the amorphous (A) and the crystalline (C) phases can be competing. The A : C ratio may vary from 30 : 70 to 70 : 30%.

If the quantity of the amorphous phase introduced during the batch preparation or formed under sintering is less than 30 – 20%, it is possible to introduce a sintering additive ensuring liquid-phase sintering [9]. In producing bioceramics, HAP is the most commonly used crystalline phase. The sintering additive consists of ions contained in the bone structure. Apart from phosphate and silicophosphate glasses, the sintering additive may be a salt, such as carbonate, phosphate, or silicate of potassium, sodium, and calcium, which in firing is transformed into an oxide melt. The main requirement imposed on the sintering additive composition is that the temperature of its effect (melting and spreading) be within the traditional sintering interval of the main phase, in our case HAP. The introduction of up to 5% phosphate glass ($CaO – P_2O_5 – Na_2O$) strengthens HAP-based ceramics [10].

The production of polycrystalline materials of the third group (mono- or polyphase materials) occurs through the sintering of a powder system of a corresponding initial composition. Such materials are characterized by the absence of a vitreous phase. The sintering of material occurs by the diffusion mechanism or with the participation of a liquid phase and its subsequent complete crystallization. The presence of TCP and PP phases in materials, similarly to the presence of phosphate glasses,makes these materials biodegradable and reabsorbable by the body.

The chemical components of extensively used additives are restricted to elements contained in natural bones. The effect of such additives as CO_3^{2-}, SiO_4^{4-}, Mg^{2+}, Zn^{2+}, $F^–$, $Cl^–$, K^+, and Na^+ introduced separately or jointly has been investigated. The introduction of some additives, for instance, Mg^{2+}, Zn^{2+}, and $F^–$, does not significantly modify the crystal structure of hydroxyapatite, since the two-charge metal ions can take the positions of the Ca^{2+} ion and fluorine ions can take the place of the $OH^–$ group. The presence of CO_3^{2-} and SiO_4^{4-} groups produces a certain modification of the structure, since these ions presumably take the place of the $(PO_4)^{3-}$ ion. Thus, the charge compensation in the carbonate-hydroxyapatite structure under the heterovalent substitution of the carbonate ion for the phosphate ion can be achieved by means of a calcium deficit and (or) substitution of sodium for calcium. Upon introducing SiO_4^{4-}, the crystal lattice of apatite can lose part of the hydroxide ions and (or) capture CO_3^{2-} that is present in the aqueous solution at pH over 7 due to dissolving carbon dioxide from air. The replacement of $OH^–$ groups by chlorine ions in the apatite structure is difficult due to the substantial size of the chlorine ion.

The role of the above listed additives in the formation of crystals from solutions and under sintering is different. The effect of external ions on the shape and size of apatite crystals synthesized from solutions is shown in Fig. 1. The effect of these additives on the properties of polycrystalline materials in the system $CaO – P_2O_5$ differs as well. The presence of

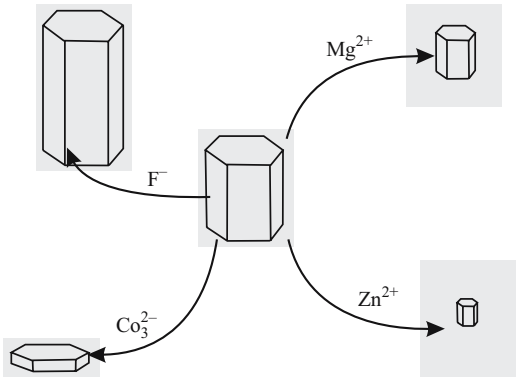

Fig. 1. The effect of different ions on the shape of hydroxyapatite crystals.

CO_3^{2-} decreases the Ca : P ratio in hydroxyapatite, increases the deficit of calcium and the defectiveness of the crystal lattice, and, consequently, facilitates sintering [11]. The synthesis of the initial powder in air to obtain HAP-based ceramics inevitably results in the material capturing CO_3^{2-}. The resulting carbonate-apatite has lower bioresistivity and higher bioactivity. The presence of F^- ions, on the contrary, yields a material with higher bioresistivity. The capture of metal or halogen ions during the synthesis of HAP is possible, for instance, from sodium or potassium phosphates [12] or from calcium chloride. It should be noted that most researchers prefer synthesizing HAP through the reaction of ammonium phosphate with calcium nitrate or calcium hydroxide suspension with phosphoric acid. These two methods of synthesis seem to eliminate the effect of byproducts and makes it possible to judge the influence of particular additives. It is assumed that the introduction of SiO_4^{4-}, Mg^{2+}, and Zn^{2+} can affect the growth of crystal grains not only in synthesis, but in sintering as well. The role of SiO_4^{4-} should be stressed. The presence of this group in the HAP structure, as was earlier observed for glass ceramics based on silicophosphate glasses, raises the bioactivity of material and facilitates the dissolution of the implant surface and the formation of a new hydroxyapatite layer in the organism.

To achieve a higher efficiency of sintering additives, they should be uniformly distributed in the material. These additives can be introduced at various stages of production: during synthesis, disintegration, introduction of the binder, or firing (introduction via a gaseous phase). The introduction of additives during the synthesis of powders appears preferable, since the degree of homogenization of the initial components is high. This approach appears optimal when the main components and the additive tend to form solid solutions. In general it can be stated that modifying the chemical composition of apatite via ionic substitution is a promising but relatively little investigated method for controlling biomedical properties of ceramics.

Control of the phase composition is a more traditional method, which is more widely implemented. However, there are reasons to assume that the potential of this approach is not yet exhausted. A desired phase composition should be formed depending on its projected medical application. Materials with a preset phase composition should have sufficient density for the desired application (be solid or porous) and strength, as well as adequate biological properties, such as bioresistivity or biodegradability at a rate consistent with the proposed treatment method. Only a combination of the methods of the phase composition formation and ionic substitution in apatite will contribute to the development of advanced ceramic biomaterials with a required set of properties.

REFERENCES

1. Yu. D. Tret'yakov (ed.), *Inorganic Chemistry, Vol. 2. Chemistry of Nontransition Elements* [in Russian], Akademiya Publishing Center, Moscow (2004).
2. T. Kanazava, *Inorganic Phosphate Materials* [Russian translation], Naukova Dumka, Kiev (1998).
3. S. M. Barinov and V. S. Komlev, *Bioceramics Based on Calcium Phosphates* [in Russian], Nauka, Moscow (2005).
4. B. I. Beletskii, V. I. Shumskii, A. A. Nikitina, and E. B. Vlasova, "Calcium phosphate biocomposite materials in osteoplastic surgery," *Steklo Keram.*, No. 9, 35 – 37 (2000).
5. P. D. Sarkisov, N. Yu. Mikhailenko, and V. M. Khavala, "Biological activity of materials based on glass and glass ceramics," *Steklo Keram.*, Nos. 9 – 10, 5 – 11 (1993).
6. G. V. Meshkov, "Combined application of ceramics implants based on hydroxyapatite and titanium fixtures in craneofacial reconstructive surgery," *Stomatologiya*, **75**(5), 35 – 42 (1996).
7. L. Hench, "Bioceramics," *J. Am. Ceram. Soc.*, **81**(7), 1705 – 1728 (1998).
8. *Knowles J. C.* "Phosphate based glasses for biomedical applications," *J. Mater. Chem.*, **13**, 2395 – 2401 (2003).
9. W. Suchanek, V. Yahima, M. Kakihana, and M. Yoshimura, "Hydroxyapatite ceramics with selected sintering additives," *Biomaterials*, **18**(13), 923 – 933 (1997).
10. G. Georgiou and J. C. Knowles, "Glass-reinforced hydroxyapatite for hard tissue surgery. Part 1. Mechanical properties," *Biomaterials*, **22**, 2811 – 2815 (2000).
11. S. Raynaud, E. Champion, and D. Bernache-Assollant, "Calcium phosphate apatites with variable Ca/P atomic ratio. Part II. Calcination and sintering," *Biomaterials*, **23**, 1073 – 1080 (2002).
12. Cuneyt A. Tas and B. Bhaduri Sarit, "Chemical processing of $CaHPO_4 \cdot 2H_2O$: Its conversion to hydroxyapatite," *J. Am. Ceram. Soc.*, **87**(12), 2195 – 2200 (2004).